UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/855,342	05/14/2001	Michael A. Caligiuri	35784/209112 (5784-50)	8842

20855 7590 04/30/2007

ROBINS & PASTERNAK
1731 EMBARCADERO ROAD
SUITE 230
PALO ALTO, CA 94303

EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
04/30/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/855,342	CALIGIURI ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-23,25-50,52,53,55,56,58,59 and 61-79* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-23,25-50,52,53,55,56,58,59 and 61-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20070221*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 15, 2007, has been entered.

1. The amendment filed February 15, 2007, is acknowledged and has been entered. Claim 24 has been canceled. Claims 12-19, 25, 29-40, 42-47, 52, 55, 58, 61, 63-65, 67, 69, and 74-79 have been amended.

2. Claims 12-23, 25-50, 52, 53, 55, 56, 58, 59, and 61-79 are pending in the application and are currently under prosecution.

Information Disclosure Statement

3. The information disclosure filed February 15, 2007, has been considered. An initialed copy is enclosed.

Priority

4. Although this application claims under 35 USC § 119(e) the earlier filing date of the U.S. Provisional Application Serial No. 60/204,284, filed May 15, 2000, claims 12-23, 25-50, 52, 53, 55, 56, 58, 59, and 61-79 do not properly benefit under 35 U.S.C. § 119(e) by the earlier filing date of the provisional application, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure.

Beginning at page 18 of the amendment filed February 15, 2007, Applicant has disagreed, asserting that, as currently amended, the claims are entitled to the claimed benefit.

Applicant's remarks have been carefully considered but are not persuasive, as the rejections of the claims under § 112, first paragraph, have been maintained for the reasons set forth below.

Grounds of Objection and Rejection Withdrawn

5. Unless specifically reiterated below, Applicant's amendment and/or arguments filed February 15, 2007, have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed November 21, 2006.

Grounds of Objection Maintained

Amendment

6. The objection to the amendment filed September 1, 2006, under 35 U.S.C. § 132(a), because it introduces new matter into the disclosure, is maintained.

Beginning at page 16 of the amendment filed February 15, 2007, Applicant has traversed the propriety of this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

As explained in the preceding Office action mailed November 21, 2006, 35 U.S.C. § 132(a) states that no amendment shall introduce new matter into the disclosure of the invention.

The added material, which appears not supported by the original disclosure, is the reference to "SEQ ID NO: 1" that has been inserted by the amendment to the specification at page 29, and the Sequence Listing disclosing the amino acid sequence of SEQ ID NO: 1.

As amended at page 29 in the paragraph beginning in line 2, the specification reads:

> The IL-2 formulation in this study is manufactured by Chrion Corporation of Emeryville, California, under the tradename Proleukin. The IL-2 in this formulation is a recombinantly produced human IL-2 mutein, called aldesleukin, which differs from the native human IL-2 sequence (SEQ ID NO:1) in having the initial alanine residue eliminated and the cysteine residue at position 125 replaced by serine (referred to as des-alanyl-1, serine-125 human interleukin-2). This IL-2 mutein is expressed from E. coli, and subsequently purified by diafiltration and cation exchange chromatography as described in U.S. Patent No. 4,931,543.

Thus, the introduction of SEQ ID NO: 1 at page 29 by the amendment defines the native human IL-2 sequence as the amino acid sequence set forth as SEQ ID NO: 1. Notably, the original disclosure at page 29 provides no apparent nexus between the amino acid sequence set forth as SEQ ID NO: 1 and the amino acid sequence of native human IL-2.

At page 15, paragraph 2, of the amendment filed September 1, 2006, Applicant has asserted that the specification, as originally filed, provides support for this amendment to the specification, since "SEQ ID NO:1 now corresponds to the sequence of native mature human IL-2 disclosed in Figure 2b of U.S. Patent No. 4,738,927, which was cited in the instant application, for example, at page 17, line 13, and incorporated by reference".

The disclosure at page 17, lines 1-14, of the specification reads as follows:

> The IL-2 or variants thereof for use in the methods of the present invention may be from any source, but preferably is recombinant IL-2. By "recombinant IL-2" is intended interleukin-2 that has comparable biological activity to native-sequence IL-2 and that has been prepared by recombinant DNA techniques as described, for example, by Taniguchi et al. (1983) Nature 302:305-310 and Devos (1983) Nucleic Acids Research 11:4307-4323 or mutationally altered IL-2 as described by Wang et al. (1984) Science 224:1431-1433. In general, the gene coding for IL-2 is cloned and then expressed in transformed organisms, preferably a microorganism, and most preferably E. coli, as described herein. The host organism expresses the foreign gene to produce IL-2 under expression conditions. Synthetic recombinant IL-2 can also be made in eukaryotes, such as yeast or human cells. Processes for growing, harvesting, disrupting, or extracting the IL-2 from cells are substantially described in, for example, U.S. Pat. Nos. 4,604,377; 4,738,927; 4,656,132; 4,569,790; 4,748,234; 4,530,787; 4,572,798; 4,748,234; and 4,931,543, herein incorporated by reference in their entireties.

Agreeably, the specification, as filed, refers to U.S. Patent No. 4,738,927, at page 17, lines 10-14, but nowhere else; and agreeably the patent has been incorporated by reference in its entirety, together with the entireties of each of U.S. Pat.

Nos. 4,604,377; 4,656,132; 4,569,790; 4,748,234; 4,530,787; 4,572,798; 4,748,234; and 4,931,543.

This disclosure, however, does not appear to provide a nexus between the amino acid sequence set forth as the corresponding amino acid sequence depicted in Figure 2B of U.S. Patent No. 4,738,927 (i.e., SEQ ID NO: 1) and the amino acid sequence of native human IL-2.

Figure 2B of U.S. Patent No. 4,738,927 depicts **three** distinct amino acid sequences, which are designated "Amino Acid Sequence 1", "Amino Acid Sequence 2", and "Amino Acid Sequence 3", and which, according to the corresponding brief description of the figure (column 3, lines 16-19), are the amino acid sequences of "the polypeptides which possess IL-2 activity".

Figure 2B of U.S. Patent No. 4,738,927 does not describe any one of the three amino acid sequences *as the sequence of the native human IL-2 molecule*.

Accordingly, contrary to Applicant's contention, the disclosure at page 17 of the specification does not appear to provide support for the added material because it does not *particularly* identify that added material, not as that contained by the disclosure of U.S. Patent No. 4,738,927, per se, and not as any particular part thereof.

According to M.P.E.P. 608.01(p):

> Mere reference to another application, patent, or publication is not an incorporation of anything therein into the application containing such reference for the purpose of the disclosure required by 35 U.S.C. 112, first paragraph. *In re de Seversky*, 474 F.2d 671, 177 USPQ 144 (CCPA 1973).

With regard to incorporation by reference, the Federal Circuit in deciding *Advanced Display Systems Inc. v. Kent State University,* 54 USPQ2d 1673 (CA FC), has further opined:

> Incorporation by reference provides a method for integrating material from various documents into a host document--a patent or printed publication in an anticipation determination--by citing such material in a manner that makes clear that the material is effectively part of the host document as if it were explicitly contained therein. *See General Elec. Co. v. Brenner*, 407 F.2d 1258, 1261-62, 159 USPQ 335, 337 (D.C. Cir. 1968); *In re Lund*, 376 F.2d 982, 989, 153 USPQ 625, 631 (CCPA 1967). To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material

> is found in the various documents. *See In re Seversky,* 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement "clearly identifying the subject matter which is incorporated and where it is to be found"); *In re Saunders*, 444 F.2d 599, 602-03, 170 USPQ 213, 216-17 (CCPA 1971) (reasoning that a rejection for anticipation is appropriate only if one reference "expressly incorporates a particular part" of another reference); *National Latex Prods. Co. v. Sun Rubber Co.*, 274 F.2d 224, 230, 123 USPQ 279, 283 (6th Cir. 1959) (requiring a specific reference to material in an earlier application in order have that material considered part of a later application); *cf. Lund*, 376 F.2d at 989, 153 USPQ at 631 (holding that a one sentence reference to an abandoned application is not sufficient to incorporate material from the abandoned application into a new application). Whether and to what extent material has been incorporated by reference into a host document is a question of law. *See Quaker City Gear Works, Inc. v. Skil Corp.*, 747 F.2d 1446, 1453-54, 223 USPQ 1161, 1166 (Fed. Cir. 1984) (reasoning that whether a document is incorporated by reference into a patent presents a question of law when determining enablement). *Id.* at 1679-1680.
>
> [Thus] the standard of one reasonably skilled in the art should be used to determine whether the host document describes the material to be incorporated by reference with sufficient particularity. *Id.* at 1680.

In this instance, the disclosure at page 17 of the specification does not provide proper written support for the added material since that material is a particular amino acid sequence disclosed as one of three in a figure in one of several patents, which is incorporated by reference but not particularly referred to as providing a disclosure of the particular amino acid sequence, which Applicant has alleged is the amino acid sequence of native mature human IL-2.

Applicant has argued that Figure 2B of U.S. Patent No. 4,738,927 clearly shows that "Sequence 2" is the mature active form of IL-2.

In response, the Brief Description of Figure 2B reads: "FIG. 2(b) shows Amino Acid Sequence I, and Amino Acid Sequences II and III, of the polypeptides which possess IL-2 activity." Contrary to Applicant's assertion, it is not evident from the disclosure that "Sequence 2", as depicted in this figure, is the mature active form of IL-2; and moreover, the disclosure does not describe any one of the three amino acid sequences depicted in the figure *as the sequence of the native human IL-2 molecule.*

Nonetheless, as explained previously, although the patent has been incorporated by reference in this application, the statement of incorporation by reference appearing in the disclosure at page 17 of the specification does not identify with requisite particularity that material that has been added to the specification by the

amendment. Additionally, the statement of incorporation by reference does not identify the specific material that has been added by the amendment, as the material that is recognized or acknowledged by the Applicant to be contained by the disclosure of U.S. Patent No. 4,738,927, per se, as opposed to any of the other numerous patents cited within the very same paragraph; and finally the statement of incorporation by reference does not identify the added material as that material, which was contained by any particular part of the patent's disclosure. It is for these reasons that the specification, as filed, and its statement of incorporation by reference of U.S. Patent No. 4,738,927, does not appear to provide adequate written support for the added material.

Applicant has argued that the structure of the human native active form of IL-2 was well known at the time the application was filed.

This argument is seemingly irrelevant. Again, the issue is not whether or not the molecule was known at the time the application was filed, but rather the specification, as filed, provides written support for the specific material that was added thereto by the amendment filed September 1, 2006.

Applicant has further argued that the specification need not recite the amino acid sequence of native human IL-2 because it was well known in the prior art.

Agreeably, the disclosure at page 29 of the specification need not recite the amino acid sequence of native human IL-2; therefore, it is suggested that this issue be remedied by canceling the added recitation of SEQ ID NO: 1 in amended paragraph at page 29 of the specification and by the provision of a substitute Sequence Listing from which the listing of the amino acid sequence of SEQ ID NO: 1 has been struck.

Applicant is required to cancel the new matter in the reply to this Office Action.

Grounds of Rejection Maintained

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. The rejection of claims 74-79 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is maintained.

Beginning at page 37 of the amendment filed February 15, 2007, Applicant has traversed the propriety of this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Claims 74-79 contain the trademark Herceptin™. Where a trademark is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark cannot be used properly to identify any particular material or product. A trademark is used to identify a source of goods, and not the goods themselves. Thus, a trademark does not identify or describe the goods associated with the trademark. In the present case, the trademark HERCEPTIN is used to identify/describe the recombinant, humanized anti-HER2 antibody derived from the murine monoclonal antibody 4D5, which is known by the generic name Trastuzumab, and accordingly the identification/description is indefinite.

Applicant has argued the use of trademarks is permissible in application under certain conditions.

In response, if the trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of the 35 U.S.C. 112, second paragraph. M.P.E.P. § 2173.05(u).

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. The rejection of claims 12-23, 25-50, 52, 53, 55, 56, 58, 59, and 61-79 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "new matter" rejection.

Beginning at page 38 of the amendment filed February 15, 2007, Applicant has traversed the propriety of this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

(a) Claims 12, 16, 17, 42, and 63 recite, "an interleukin-2 (IL-2) polypeptide comprising SEQ ID NO: 1".

As explained in the preceding Office action, contrary to Applicant's assertion the specification, as filed, does not provide written support for the language of the claims.

As presently amended at page 29 in the paragraph beginning in line 2, the specification reads:

> The IL-2 formulation in this study is manufactured by Chrion Corporation of Emeryville, California, under the tradename Proleukin. The IL-2 in this formulation is a recombinantly produced human IL-2 mutein, called aldesleukin, which differs from the native human IL-2 sequence (SEQ ID NO:1) in having the initial alanine residue eliminated and the cysteine residue at position 125 replaced by serine (referred to as des-alanyl-1, serine-125 human interleukin-2). This IL-2 mutein is expressed from E. coli, and subsequently purified by diafiltration and cation exchange chromatography as described in U.S. Patent No. 4,931,543.

Thus, the introduction of SEQ ID NO: 1 at page 29 by the amendment defines the native human IL-2 sequence as the amino acid sequence set forth as SEQ ID NO: 1.

Thus, while the inclusion of SEQ ID NO: 1 in the claims finds support in the specification, *as amended September 1, 2006*, the original disclosure provides no apparent nexus between the amino acid sequence set forth as SEQ ID NO: 1 and the amino acid sequence of the native human IL-2 molecule, which might serve as a basis for the amendment to the specification. If, as explained above, the amendment to the

specification finds no written support in the specification, including the claims, as originally filed, then amending the claims to recite "SEQ ID NO: 1" introduces new matter and thereby violates the written description requirement set forth under 35 U.S.C. § 112, first paragraph.

Applicant has argued that the specification need not recite the sequence to which the claims are directed.

The Examiner disagrees. The language of the claims must find clear and particular written support in the disclosure. If the claims are directed to a particular amino acid sequence (e.g., SEQ ID NO: 1), the disclosure must describe that sequence with clarity and particularity. Therefore, because the instant claims are directed to an IL-2 polypeptide comprising the sequence of SEQ ID NO: 1, the disclosure must describe such polypeptides comprising the amino acid sequence of SEQ ID NO: 1.

Applicant has argued that the specification need not incorporate by reference a particular sequence that is not disclosed in specification but which is recited in the claims, if the sequence is known in the prior art.

The Examiner disagrees. If claims are directed to a particular amino acid sequence (e.g., SEQ ID NO: 1), the recited sequence is essential material that must be disclosed in the specification. "Essential material" is defined as "that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best mode (35 U.S.C. 112)". See M.P.E.P. § 608.01(p). While the M.P.E.P. does not provide for the incorporation by reference of essential material by reference to non-patent publications, it is properly incorporated by reference to patents, *but the statement of incorporation must make evident the particular material that is to be incorporated.* In this instance, as explained above, the language of the rejected claims does not find proper antecedent basis in the specification, as originally filed, and the amendment thereof, which was filed September 1, 2006, to remedy that deficiency, improperly introduces new matter, thereby violating the requirement set forth under 35 U.S.C. § 132. As a consequence, the present claims do not find written support in the specification, as filed, and the recitation of "an interleukin-2 (IL-2)

polypeptide comprising SEQ ID NO: 1" has introduced new concepts, violating the written description requirement set forth under § 112, first paragraph.

(b) Claims 12, 16, 17, and 42 recite "an interleukin-2 (IL-2) polypeptide comprising the sequence of SEQ ID NO:1 or a biologically active variant thereof [...] wherein said variant of IL-2 has anti-tumor activity and at least 90% sequence identity to SEQ ID NO: 1".

As explained in the preceding Office action, contrary to Applicant's assertion the specification, as filed, does not provide written support for the language of the claims.

At page 14, lines 11-14, the specification discloses, "biologically active variants of IL-2 will generally have at least 70%, preferably at least 80%, more preferably about 90% to 95% or more, and most preferably about 98% or more amino acid sequence identity to the amino acid sequence *of the reference polypeptide molecule, which serves as the basis for comparison*" (italicized for added emphasis).

Thus, this disclosure describes biologically active variants of "IL-2", which generally have at least 90% amino acid sequence identity to the amino acid sequence of the reference polypeptide, which serves as the basis of comparison. The term "IL-2" is explicitly defined in the specification at page 12, lines 8 and 9, to mean: "A lymphokine that is produced by normal peripheral blood lymphocytes and is present in the body at low concentrations". At page 12, lines 9-14, the specification further describes "IL-2" as first described by Morgan et al. (1976) and originally called T cell growth factor because of its ability to induce proliferation of stimulated T lymphocytes, and is a protein with a reported molecular weight in the range of 13,000 to 17,000 (Gillis and Watson (1980)) and has an isoelectric point in the range of 6-8.5.

However, the particular disclosure at page 14 of the specification does not provide written support for variants of a polypeptide comprising the amino acid sequence of SEQ ID NO: 1, per se, nor does it provide written support for variants of such a polypeptide comprising amino acid sequences that are at least 90% identical to amino acid sequence of that polypeptide (i.e., SEQ ID NO: 1). Moreover, it appears that the specification only provides written support for suitable biologically active variants of native and naturally occurring IL-2, including "fragments", analogues", and "muteins", as

opposed to variant of an IL-2 molecule comprising the amino acid sequence of SEQ ID NO: 1; see, in particular, page 13, lines 6 and 7.

Applicant has argued that the amendment to claims 12, 16, 17, and 42 has obviated this issue because the recited variants of IL-2 have at least 90% sequence identity to SEQ ID NO: 1.

The Examiner disagrees; this issue has not been remedied by the amendment to the claims. As explained, the specification only provides written support for suitable biologically active variants of native and naturally occurring IL-2, including "fragments", analogues", and "muteins". The specification does not provide written support for variants of an IL-2 molecule comprising the amino acid sequence of SEQ ID NO: 1.

11. The rejection of claims 12-23, 25-50, 52, 53, 55, 56, 58, 59, and 61-78 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, is maintained.

This is a "written description" rejection.

Beginning at page 19 of the amendment filed February 15, 2007, Applicant has traversed the propriety of this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant has remarked that the burden is on the Examiner to provide evidence as to why a skilled artisan would not have recognized that the Applicant was in possession of the claimed invention at the time the application was filed.

In response, the considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, "Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

With further regard to the proposition that, as *original* claims, the language of those claims themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, while an original claim may provide written description for itself, it must still find an adequate written description in the specification, *which establishes that the inventor was in possession of the invention*. In this instance, there is a preponderance

of factual evidence now of record, which indicates that the specification would not have reasonably conveyed Applicant's possession of the subject matter that is now claimed.

For example, as noted at page 35 of the Office action mailed March 2, 2006:

> [A]part from Herceptin™, it appears the specification fails to describe an antibody that is *not* conjugated to a toxin moiety (e.g., a radionuclide or chemotherapeutic agent), which inhibits the growth of cancer cells *in vivo*. Inasmuch as the clinical effectiveness of Herceptin™ (i.e., a naked recombinant humanized version of murine monoclonal antibody 4D5) appears *unique*, it is noteworthy that the specification fails to describe the genus of antibodies to which the claims are directed as binding specifically to the same "epitope" of HER2 as monoclonal antibody 4D5 and Herceptin™. Moreover, the specification does not describe the one, or possibly more "epitopes" to which the genus of antibodies must bind, if not conjugated to a cytotoxic moiety, so as to yield the claimed therapeutic effect *in vivo* during the practice of the claimed invention.

Additionally, as explained at page 34 of this Office action, only the *recombinant humanized* version of the murine antibody (i.e., Herceptin™ (Trastuzumab)) has been shown to mediate ADCC; murine monoclonal antibody 4D5 does not. Accordingly, it is not by mere virtue of the epitope to which an antibody binds that the antibody has such activity.

Then, as explained in the Office action mailed February 18, 2005, Lewis et al. (of record) teaches murine monoclonal antibody 4D5 does not affect the proliferation of gastric and colon cancer cells, even though these cells express an amount of HER2 that is equivalent to the amount expressed by breast cancer cells that are sensitive to the effects of treatment with the antibody. It is not by mere virtue of the epitope to which an antibody binds that the antibody has anti-proliferative effects upon cancer cells expressing HER2.

Additionally, as also explained previously, even though the prior art teaches monoclonal antibody 520C9 is capable of mediating ADCC, its ability to do so appears relatively unique and its use *in vivo* to achieve therapeutic benefit in treating cancer overexpressing HER2 has apparently not been reported; see, e.g., pages 14 and 15 of the preceding Office action mailed February 18, 2005.

Furthermore, while the art teaches that an immunotoxin comprising monoclonal antibody 520C9 can be used to inhibit the growth of tumor cells, again, there appear no reports that the monoclonal antibody itself, or any fragment thereof, is capable of

effectively inhibiting the growth of tumor cells *in vivo*. In fact, seemingly to the contrary, Keler et al. (of record) demonstrates the $F(ab')_2$ fragment of monoclonal antibody 520C9 is relatively incapable of mediating ADCC compared to MDX-H210, a recombinant bispecific antibody comprising a Fab' fragment of 520C9. It is not by mere virtue of the epitope to which an antibody binds that the antibody has anti-proliferative effects upon cancer cells expressing HER2.

Moreover, regardless of the specific epitope to which the anti-HER2 antibody binds, as further explained in the preceding Office actions, few *naked* antibodies have been described which are capable of achieving clinically or therapeutically significant benefits in treating cancer. As mentioned above, Herceptin™ seems the notable exception, inasmuch as it has been shown clinically effective, alone and/or in combination with other anticancer drugs, to inhibit the growth of breast cancer characterized by the overexpression of HER2.

Then, with regard to claims 12, 16, and 42, which are directed to a genus of antibodies having "anti-tumor activity", as well as a genus of biologically active variants of an IL-2 molecule comprising the amino acid sequence of SEQ ID NO: 1, which have "anti-tumor" activity.

As previously noted, at page 4, lines 11-22, the specification discloses the following:

> By "anti-tumor activity" is intended a reduction in the rate of cell proliferation, and hence a decline in growth rate of an existing tumor or in a tumor that arises during therapy, and/or destruction of existing neoplastic (tumor) cells or newly formed neoplastic cells, and hence a decrease in the overall size of a tumor during therapy.

The antibodies to which the claims are directed necessarily bind to the extracellular domain of HER2[1], but are nonetheless structurally unrelated.

The biologically active variants of the IL-2 molecule to which the claims are directed must comprise an amino acid sequence having at least 90% identity to SEQ ID

[1] As the claims are presently amended, the anti-HER2 antibodies comprise a CDR of monoclonal antibody 4D5 or monoclonal antibody 520C9, but need not bind to the same epitope of HER2 as either monoclonal antibody.

NO: 1, as calculated in accordance with the claims, but nonetheless vary in their structures.

Notably, the members of the genus of antibodies to which the claims are directed and the members of the genus of biologically active variants of an IL-2 molecule comprising the amino acid sequence of SEQ ID NO: 1 are not structurally related; yet, according to the claims, they possess the same anti-tumor activity.

These facts illustrate a lack of correlation between any one particularly identifying (i.e., substantial) structural feature and any one particularly identifying functional feature, which, if otherwise disclosed, would permit the skilled artisan to immediately envision, recognize or distinguish the antibodies and the biologically active variants of the IL-2 molecule comprising SEQ ID NO: 1 to which the claims are directed.

As previously explained, "generalized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004). In this instance, there is no language that adequately describes the genus of anti-HER2 antibodies having anti-tumor activity, which when *not* conjugated to a cytotoxic moiety, inhibit the growth of cancer cells, so as to achieve the claimed effect. Similarly, there is no language that adequately describes the genus of biologically active variants of an IL-2 molecule comprising amino acid sequence of SEQ ID NO: 1 having anti-tumor activity, which when administered in combination with the antibody inhibits the growth of cancer cells, so as to achieve the claimed effect. *A description of what a material does, rather than of what it is, does not suffice to describe the claimed invention.*

Again, the Federal Circuit has decided that a generic statement that defines a genus of substances by *only* their functional activity does not provide an adequate written description of the genus. See *The Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997).

As further explained in the preceding Office action, although *Lilly* related to claims drawn to genetic material, the statute applies to all types of inventions. "Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he

can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1984 (CAFC 2004). Without the antibody and the biologically active variant of an IL-2 molecule comprising the amino acid sequence of SEQ ID NO: 1, it is impossible to use the claimed invention.

Although the skilled artisan could potentially screen candidate anti-HER2 antibodies and variants of the IL-2 molecule comprising SEQ ID NO: 1 to identify those that might be used in practicing the claimed invention to achieve the claimed effect, again, the written description provision of 35 U.S.C. § 112 is severable from its enablement provision. See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991); *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

As an additional matter necessitated by the amendment, claims 12, 16, 17, and 42 are presently directed to a genus of antibodies having anti-tumor activity, which bind to the extracellular domain of HER2, though not necessarily to the same epitope as an antibody selected from the group consisting of 4D5 and 520C9. However, as noted above, inasmuch as the epitope to which the antibody binds does not suffice to determine the effectiveness of the antibody to inhibit the growth of cancer cells, its ability to bind to any given epitope of the extracellular domain of HER2 does not either; consequently, there is no correlation between the ability of an antibody to bind to any one epitope of the extracellular domain of HER2, or more particularly either one of the epitopes recognized by monoclonal antibodies 4D5 or 520C9, and its ability to act effectively as an inhibitor of the growth or proliferation of breast cancer cells. Therefore, even if one were capable of recognizing or distinguishing antibodies that bind to one or another epitope of the extracellular domain of HER2, it would still not be possible to immediately envision, recognize, or distinguish those suitable for use in practicing the claimed invention to achieve the claimed therapeutic effect.

Furthermore, for the reasons explained in the preceding Office action, and despite any presumption otherwise, the instant disclosure would not provide a written

description of the claimed invention, which would suffice to permit the skilled artisan to immediately envision, recognize or distinguish antibodies that bind the same epitope of the extracellular domain of HER2, which is recognized by either monoclonal antibody 4D5 or 520C9.

As observed in the preceding Office action, the Federal Circuit recently decided that the description of a fully characterized molecular target of an antibody is sufficient to adequately describe an antibody that binds that target. See *Noelle v. Lederman*, 69 USPQ2d 1508 (CA FC 2004). However, the same court decided that each case involving the issue of written description, "must be decided on its own facts. Thus, the precedential value of cases in this area is extremely limited." *Vas-Cath*, 935 F.2d at 1562 (quoting *In re Driscoll*, 562 F.2d 1245, 1250 (C.C.P.A. 1977)).

Following the example set by the Federal Circuit in deciding *Noelle v. Lederman*, *were* the claims directed to an antibody that binds a well-characterized antigen, the written description would be met. In this instance, however, the claims are not directed to an antibody that binds a well-characterized molecular target, but rather to an antibody that binds to the very discrete parts (i.e., epitopes) of HER2 to cause a very particular effect (i.e., the inhibition of the growth of the breast cancer cell overexpressing HER2).

In addition, as explained above, there is factual evidence that the detailed description of an antigen, as opposed to the detailed description of an epitope of an antigen, should not always be regarded as sufficient to describe the antibody that binds that antigen, particularly in instances where binding of the antibody modulates the activity of the antigen or affects the growth of a cell expressing the antigen. For example, Stancoviski et al. (of record) characterized the binding effects of different anti-HER2 antibodies, which bind different epitopes of the antigen, upon the growth of tumor cells; see entire document (e.g., the abstract). Stancovski et al. teaches some anti-ErbB2 antibodies inhibited tumor cell growth, but others actually accelerated their growth (page 8693, column 1). Accordingly, the mere generalized description of antibodies that bind a well-characterized antigen, as opposed to a well-characterized epitope of an antigen, cannot always suffice to describe adequately antibodies that have, for example, an inhibitory or therapeutic effect, because the skilled artisan could

not immediately envision, recognize, or distinguish those antibodies that bind an antigen on tumor cells and inhibit the growth of those tumor cells from antibodies that bind the antigen but lack therapeutic effect (e.g., promote the growth of tumor cells). In this instance, the claims are directed to antibodies that are useful in inhibiting the growth of tumor cells expressing HER2, which are suitable for use in practicing the claimed invention to achieve the claimed therapeutic effect.

As a new matter necessitated by the amendment filed February 15, 2007, claims 12, 16, 17, and 42 are directed to a genus of anti-HER2 antibodies that bind to the extracellular domain of HER2, but which are merely described as comprising one of the complementarity determining regions (CDRs) of either monoclonal antibody 4D5 or monoclonal antibody 520C9. Thus, the genus is directed to a genus of antibodies that have a common binding specificity, but which have structures that vary substantially.

Mariuzza et al (*Annu. Rev. Biophys. Biophys. Chem.* **16**: 139-159, 1987) reviews the structural basis of antigen-antibody recognition is reviewed. A naturally occurring antibody comprises two polypeptides, the so-called light and heavy chains. The antigen-combining site of an antibody is a three-dimensional structure, which fully comprises six "complementarity-determining regions" (CDRs), three each from the light and heavy chains. The amino acid sequences of the CDRs are hypervariable, as the amino acid residues contained within the CDRs determine much of antibody's antigen-binding specificity. Of the amino acid residues of the antibody contacting the antigen, six are within the light chain, nine are within the heavy chain, and two are within the constant or nearly constant "framework" regions.

Thus, an antibody comprising only one of the six CDRs of which either monoclonal antibody 4D5 or monoclonal antibody 520C9 will not necessarily bind HER2; if does so, it will not necessarily bind the same epitope of HER2 as either of the monoclonal antibodies.

The prior art teaches well-known and conventional methodology for "humanizing" monoclonal antibodies. For example, Gussow et al. (Methods in Enzymology. 1991; 203: 99-121) teach the general methodology for making humanized antibodies; see entire document. One means for producing a humanized antibody involves grafting the

six CDRs from the light and heavy chain variable regions from a murine antibody into the framework of a human antibody. However, in general, if only one or two of the CDRs from either the light or heavy chain variable region were to be grafted, but not all three, the resultant antibody would not be expected to retain the binding affinity and specificity of the parent antibody.

Thus, while the prior art teaches some understanding of the structural basis of antigen-antibody recognition and conventional methodology for humanizing monoclonal antibodies, it is aptly noted that the art is characterized by a high level of unpredictability, since the skilled artisan still cannot accurately and reliably predict the consequences of amino acid substitutions, insertions, and deletions in the antigen-binding domains and surrounding framework regions of antibodies. For example, Giusti et al. (*Proc. Natl. Acad. Sci. USA.* 1987 May; **84** (9): 2926-2930) teaches the specificity and affinity of an antibody is exquisitely sensitive to amino acid substitutions within the primary structure of the antibody, since only a single amino acid substitution in the heavy chain of an antibody completely altered the binding specificity of an antibody that binds phosphocholine, such that the altered antibody fails to bind phosphocholine but instead binds DNA; see entire document (e.g., the abstract). Chien et al. (*Proc. Natl. Acad. Sci. USA.* 1989 Jul; **86** (14): 5532-5536) teaches that significant structural and functional changes in an antigen-binding site can be caused by amino acid substitutions in the primary structure of an antibody, including substitutions as a site remote from the complementarity determining regions of the antigen-binding domain; see entire document (e.g., the abstract). Similarly, but more recently, Caldas et al. (*Mol. Immunol.* 2003 May; **39** (15): 941-952) teaches an unexpected effect of substituting a framework residue upon binding specificity during the humanization of an antibody that binds CD18; see entire document (e.g., the abstract).

Again, while the claim language may find support in the specification, as originally filed[2], the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written

description requirement. See *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Furthermore, a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568). As evidenced by the references cited in the paragraphs above, it is apparent that the art is unpredictable; the skilled artisan cannot know whether a variant of an antibody comprising only a single CDR of an antibody having known binding specificity, as opposed to each of six, will retain that binding specificity.

So, since claims 12, 16, 17, and 42 are directed to a genus of anti-HER2 antibodies that bind to the extracellular domain of HER2, but which are merely described as comprising one of the complementarity determining regions (CDRs) of either monoclonal antibody 4D5 or monoclonal antibody 520C9, the genus is not described with the requisite particularity to satisfy the written description requirement. Though the genus of antibodies has a common binding specificity, the members of the genus have widely varying structures; and because there is no particularly identifying (i.e., substantial) structural feature that is shared by at least most of members of the genus, which correlates with their common functional feature, the description of the genus, as a whole, would not permit the skilled artisan to immediately envision, recognize or distinguish members of the genus from other antibodies. Consequently, the specification would not reasonably convey Applicant's possession of the claimed invention at the time the application was filed.

It is again noted for clarity that claims 74 and 79 have not been rejected as lacking sufficient written description, because claim 74 is directed to the method of claim 12 for treating breast cancer characterized by the overexpression of HER2, wherein

---

[2] See, e.g., paragraphs [0050]-[0056] of the published application, i.e., U.S. Patent Application Publication

said anti-HER2 antibody is Herceptin™ and said IL-2 polypeptide comprises the amino acid sequence of SEQ ID NO: 1 or is des-alanyl-1, serine-125 human interleukin-2 (i.e., aldesleukin), whereas claim 79 is directed to the method of claim 63 for treating breast cancer characterized by the overexpression of HER2, wherein said anti-HER2 antibody is Herceptin™.

12. The rejection of claims 12-23, 25-50, 52, 53, 55, 56, 58, 59, 61-73, and 75-78 under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for** using a method for treating a patient diagnosed with breast cancer that overexpresses HER2 comprising administering to the patient a therapeutically effective amount of Herceptin™ (Trastuzumab) or an immunotoxin comprised of a humanized version of murine antibody 4D5, murine antibody 520C9, or another anti-HER2 antibody, as taught by the prior art, in combination with a therapeutically effective amount of naturally occurring human IL-2, Proleukin™ (Aldesleukin), or another recombinant human "IL-2" molecule effective to stimulate non-specific immune response in humans, as taught by the prior art, **does not reasonably provide enablement for** using a method for treating a subject having breast cancer that is characterized by overexpression of HER2 according to the claims, is maintained. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Beginning at page 23 of the amendment filed February 15, 2007, Applicant has traversed the propriety of this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

As noted previously, M.P.E.P. § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to

> practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

Contrary to Applicant's assertions careful consideration of these factors indicates the claimed invention could not be used without undue and/or unreasonable experimentation.

As explained in the preceding Office actions, the references cited in support of the Office's position (e.g., Stancovski et al; Lewis et al.) clearly indicate the skilled artisan cannot reliably and accurately predict which antibodies that binds the extracellular domain of HER2 ameliorate or aggravate disease symptoms in a subject afflicted with cancer, since it is not possible to predict which of such antibodies will inhibit or enhance the growth of cancer cells, and which will have no effect. Moreover, the skilled artisan cannot predict whether any given antibody that binds to the extracellular domain of HER2, even an antibody that binds to the same epitope as either of monoclonal antibody 4D5 or 520C9, can be used in practicing the claimed invention to achieve the claimed therapeutic effect. Reimer et al. (of record), for example, teaches the diverse biological effects of anti-HER2 antibodies depends upon their varying epitope specificities; but, as explained in the above "written description"

rejection, it is not by mere virtue of the epitope to which an antibody binds that the antibody has anti-proliferative effects upon cancer cells expressing HER2. For example, while Herceptin™ is capable of inducing ADCC, the parental, murine monoclonal antibody, designated 4D5, lacks this capability; yet, as noted in the preceding Office action, it appears from Applicant's disclosure that any greater effectiveness of the exemplified combination, per se, of Herceptin™ (i.e., Trastuzumab, a recombinant humanized version of murine monoclonal antibody 4D5) and Proleukin™ (i.e., Aldesleukin, a recombinant human IL-2 mutein), as compared to that of the monotherapeutic use of the antibody, would depend upon the ability of the antibody to mediate antibody-dependent cell cytotoxicity (ADCC).

As further explained in the preceding Office action, the concept of treating cancer by coadministering IL-2 and an antitumor monoclonal antibody capable of inducing antibody-dependent cellular cytotoxicity is not novel; for example, as early as 1988 investigators, such as Kawase et al. (of record) were using such combined therapy to treat lymphokine-activated killer-resistant tumors in mice.

If the effectiveness of the exemplary combination of Herceptin™ and Proleukin™ is not dependent upon the ability of the antibody to mediate ADCC, then, the presence of IL-2-activated effector cells would not be expected to enhance the antiproliferative, i.e., therapeutic, effect of an anti-HER2 antibody.

However, the claims are not limited to any such proven combination, but are instead more broadly directed to a combination of any member of a genus of anti-HER2 antibodies that bind the extracellular domain of HER2, albeit not necessarily the same epitope of HER2 as either monoclonal antibody 4D5 or 5290C9, and an IL-2 molecule comprising the amino acid sequence of SEQ ID NO: 1 or any biologically active variant thereof comprising a similar amino acid sequence.

As has been explained, the recombinant humanized version of the murine monoclonal antibody 4D5, namely Herceptin™ has been shown to mediate ADCC; and the conventional wisdom in the art is that it is by this mechanism, albeit not by this mechanism alone, that Herceptin™ mediates its growth inhibitory effects upon tumors in

patients. However, Lewis et al. (of record) teaches that the *murine* monoclonal antibody does not mediate ADCC, and is further incapable of fixing complement to mediate complement-mediated cell cytotoxicity. Thus, if by no other mechanism Herceptin™ achieves its effectiveness, the teachings of Lewis et al. suggest that because the murine antibody does not mediate ADCC, a murine anti-HER2 antibody that binds the extracellular domain of HER2, even one that binds to the same epitope as monoclonal antibody 4D5, cannot be used in practicing the claimed invention to achieve the claimed therapeutic effect before first determining whether the antibody effectively inhibits the growth of cancer cells in patients by some other mechanism and whether administering IL-2 in combination with the antibody will enhance or perturb this mechanism.

As has also been explained in the preceding Office action, Stancovski et al. (of record) teaches none of the disclosed anti-HER2 antibodies, which inhibited the growth of tumor cells, mediated ADCC. Thus, these teachings suggest the mechanism by which mouse anti-HER2 antibodies typically affect the proliferation of cells is not effector cell (e.g., NK cell)-dependent, and further suggests that monoclonal antibody 520C9, as a murine antibody, is unusual in its ability to mediate ADCC.

For these reasons, it is submitted that murine anti-HER2 antibodies, including mouse monoclonal antibody 4D5 or any other non-human antibody that binds the same epitope of the extracellular domain of HER2, should not generally be regarded as suitable for use in the practice of the claimed invention, since most murine antibodies lack the ability to mediate ADCC in humans and are therefore not therapeutically equivalent to Herceptin™.

Furthermore, even though monoclonal antibody 520C9 is capable of mediating ADCC, it use in practicing the claimed invention to achieve the claimed therapeutic effect in patients afflicted with breast cancer has not been exemplified or otherwise demonstrated.

Again, while the art teaches that a bispecific recombinant antibody comprising an antigen-binding fragment of monoclonal antibody 520C9 and an immunotoxin comprising the antibody are capable of inhibiting the growth of tumor cells, the prior art

does not teach that monoclonal antibody 520C9 itself, or any fragment thereof, is capable of effectively inhibiting the growth of tumor cells *in vivo*. To the contrary, Keler et al. (of record) teaches the $F(ab')_2$ fragment of monoclonal antibody 520C9 is relatively incapable of mediating ADCC, as compared to MDX-H210, a recombinant bispecific antibody comprising a Fab' fragment of 520C9.

Furthermore, as explained previously, it has long been known that the ability of an antitumor antibody to induce ADCC and complement-mediated cell cytotoxicity is at least partially dependent upon the isotype of the antibody. For example, Masui et al. (of record) teaches anti-EGFR antibodies mediate antitumor effects by different mechanisms, which are at least partially determined by the different isotypes of these antibodies; and more recently, Kim et al. (of record) determined using anti-HER2 antibodies that both isotype *and epitope specificity* are important determinants of the antitumor effect of the antibodies.

More particularly, Kim et al. (of record) teaches none of the antibodies specific for one of two epitopes suppressed the growth of cancer cells *in vivo*, despite the fact that these antibodies had demonstrated considerable antitumor activity *in vitro*. In contrast, Kim et al. teaches each of the antibodies specific for the other epitope showed antitumor activities *in vivo*. Kim et al. discloses, "[i]t was surprising that HRT G2b [i.e., the antibody of IgG2b isotype] was most effective among the HRT isotype antibodies *in vivo*, whereas the HRT G2a [i.e., the antibody of IgG2a isotype] showed only a slight effect" (page 433, column 1). Kim et al. concludes the results of the *in vivo* studies could not be explained by the results obtained from the *in vitro* studies, which suggests the antitumor effects of these antibodies might involve still other mechanisms not yet identified or understood. Nevertheless, Kim et al. teaches their results clearly indicate that the epitope specificity of antitumor antibodies, in addition to their isotypes, determines their ability to exert effective antitumor activity both *in vitro* and *in vivo* (page 433, column 1). Given the complexity and unpredictability made evident by the teachings of Kim et al., it is submitted that the skilled artisan could not practice of the claimed invention without undue and/or unreasonable experimentation.

As previously explained, it is not sufficient to merely know that an antibody binds the extracellular domain of HER2, or even to the same epitope of the antigen as another antibody, as it cannot be predicted whether the antibody will be effective to inhibit cancer cells. Moreover, in light of Kim et al., it is also not sufficient to merely know that an antibody that binds the extracellular domain of HER2 is capable of mediating ADCC or CDC *in vitro*, as it cannot be predicted whether the antibody will be effective *in vivo*. Kim et al. also underscores the conclusions that have been made on the basis of the teachings of Stancovski et al. and Lewis et al.; Kim et al. also teaches the epitope specificity is an important determinant of the antitumor activity of an anti-HER2 antibody.

Further demonstrating this complexity, as well as the unpredictability in this area of the art, Vuist et al. (of record) teaches treatment of cancer cells with an antitumor antibody of the isotype IgG2a was therapeutically active by itself; however, Vuist et al. teaches IgG1 and IgG2b isotype variants of this antitumor antibody were not active alone to inhibit the growth of the cells. As noted in the preceding Office action, although both IgG1 and IgG2b isotype variants were ineffective alone, Vuist et al. teaches their combination with recombinant IL-2 resulted in significant antitumor effects. The antibody of IgG2a isotype, which was effective alone, was more so in combination with recombinant IL-2. Vuist et al. discloses further characterization of these antibodies using *in vitro* studies suggests the isotypes that were ineffective alone (i.e., IgG1 and IgG2b) mediated IL-2-induced ADCC activity of lymphocytes in the presence of IL-2. Vuist et al. speculates that in the presence of IL-2 the antitumor activity of the antibody of IgG2a isotype may involve both IL-2-induced ADCC activity of lymphocytes and IgG2a-restricted antitumor activity of monocytes/macrophages. Thus, contrasting other disclosures, such as Kim et al. (*supra*), Vuist et al. provides factual evidence that mere knowledge of the isotype of an antitumor antibody does not provide a fair indication that the antibody in combination with IL-2 will be capable of mediating ADCC *in vivo*, so as to be therapeutically effective and useful in the practice of the claimed invention. Furthermore, the teachings of Vuist et al. suggest mere identification of anti-HER2 antibodies capable of inhibiting the growth of cancer cells will not provide reliable

indication that the antibody can or cannot be used in combination with IL-2 to treat cancer *in vivo*, since Vuist et al. discloses effective treatment of cancer cells with antibodies, which were not effective alone, in the presence of IL-2.

Additionally, regardless of the specific epitope of the extracellular domain of HER2 to which the anti-HER2 antibody binds, few *naked* antibodies have been described which are capable of achieving clinically or therapeutically significant benefits in treating cancer. Again, Herceptin™ seems the notable exception, inasmuch as it has been shown clinically effective, alone and/or in combination with other anticancer drugs, to inhibit the growth of breast cancer characterized by the overexpression of HER2.

Yet, while the claims are directed to an antibody that binds to the same epitope as monoclonal antibody 4D5, the claims are not limited to humanized versions of the monoclonal antibody, such as Herceptin™, which are known or expected to have the capability of inducing ADCC in humans.

Furthermore, as also explained in the "written description" rejection and again above, even though the prior art teaches monoclonal antibody 520C9 is capable of mediating ADCC, its ability to do so appears relatively unique; and while the prior art teaches that an immunotoxin comprising this antibody can be used to inhibit the growth of tumor cells, there are no reports that the monoclonal antibody itself, or any fragment thereof, is capable of effectively inhibiting the growth of tumor cells *in vivo*. Once again, Keler et al. (of record) demonstrated the $F(ab')_2$ fragment of monoclonal antibody 520C9 is relatively incapable of mediating ADCC compared to MDX-H210, a recombinant bispecific antibody comprising a Fab' fragment of 520C9. Therefore, again, it should not be said an anti-HER2 antibody has anti-proliferative effects upon cancer cells expressing HER2 as a mere consequence of its epitope binding specificity.

Accordingly, the references indicate that merely knowing that a given antibody binds the extracellular domain of HER2, or even to any one particular epitope of the antigen will not suffice to enable the skilled artisan to use the claimed invention to treat cancer in a subject without undue and/or unreasonable experimentation. Instead, it would first be necessary to determine *if* the antibody is effective to inhibit the growth of breast cancer cells characterized by the overexpression of HER2 *in vivo*.

While it may be a matter of routine to screen anti-HER2 antibodies that bind the extracellular domain of HER2 to identify those that are capable of inhibiting the growth of breast cancer cells characterized by the overexpression of HER2 *in vitro*, the claims are notably not drawn to such antibodies. Rather the claims are drawn to a method for treating such cancers in a subject by administering such antibodies in combination with IL-2 or a biologically active variant thereof.

The references cited in the preceding Office action establish the fact that given the level of knowledge and skill in the art the disclosure would not been reasonably enabling of the claimed invention, as the skilled artisan could not make and/or use the claimed invention without first performing the undue and/or unreasonable experimentation that would be necessary to determine *if* the claimed invention can be used to achieve the claimed therapeutic effect. For example, given the knowledge and skill in the art, while the specification reasonably enables the use of a method for treating a patient diagnosed with breast cancer that overexpresses HER2, said method comprising administering to the patient a therapeutically effective amount of Herceptin™ (Trastuzumab) in combination with a therapeutically effective amount of Proleukin™ (Aldesleukin), the claims are directed to methods for treating such cancer comprising administering any antibody that binds to the same epitope as either of the monoclonal antibodies 4D5 or 520C9 together with an IL-2 molecule comprising the amino acid sequence of SEQ ID NO: 1 or any biologically variant thereof comprising an amino acid sequence that is at least 90% identical to SEQ ID NO: 1.

M.P.E.P. § 2164.08 states, "the scope of enablement must only bear a 'reasonable correlation' to the scope of the claims" to satisfy the enablement provision set forth under 35 U.S.C. § 112, first paragraph. However, in this instance, given the disparity in the scope of enablement and the scope of the claims, it is submitted the former does not bear "reasonable correlation" to the latter.

In this instance, the claims are directed to a genus of antibodies, which bind to one or another epitope of the extracellular domain of HER2, albeit not necessarily the epitopes recognized by monoclonal antibody 4D5 or 520C9. Nevertheless, it is aptly

noted that, because the epitopes to which these particular antibodies bind have not been described, as explained in the "written description" rejection, the skilled artisan could not "make" (e.g., select) an antibody that binds to either of the same epitopes recognized by these monoclonal antibodies without undue and/or unreasonable experimentation. As taught by Greene et al. (*supra*), the epitope to which any given antibody binds must be empirically determined; so, to determine whether any one antibody binds the same epitope as another antibody would require separate determinations of both epitopes. Only after such determinations were made would it then be possible to distinguish an antibody that binds HER2 binds by recognizing the same epitope as one of the epitopes recognized by monoclonal antibody 4D5 and 520C9.

As an additional matter, whereas the previous claims were directed to a genus of variants of an IL-2 molecule, which activate NK cells, the present claims are directed to a different genus of molecules comprising an amino acid sequence that is at least 90% identical to SEQ ID NO: 1, which have "anti-tumor activity. As would be understood given the above mentioned definition of the term "anti-tumor activity", these biologically active variants of IL-2 are necessarily capable of causing a reduction in the rate of cell proliferation, and hence a decline in growth rate of an existing tumor or in a tumor that arises during therapy, and/or causing the destruction of existing neoplastic (tumor) cells or newly formed neoplastic cells, and hence a decrease in the overall size of a tumor during therapy. Accordingly, if by no other means, the biologically active variants of the IL-2 molecule comprising SEQ ID NO: 1 to which the claims are directed would have to be made and then selected upon the basis of very complicated *in vivo* experiments designed to determine whether the molecules could be used effectively to cause a reduction in tumor growth and/or tumor burden. Inasmuch, as this is the very intent for which the claimed invention is to be practiced, it is submitted the claimed invention cannot be used without undue and unreasonable experimentation, as it would require the practitioner to first elaborate a means for practicing the invention to achieve the claimed therapeutic effect.

As a new matter necessitated by the amendment filed February 15, 2007, claims 12, 16, 17, and 42 are directed to a genus of anti-HER2 antibodies that bind to the extracellular domain of HER2, but which are merely described as comprising one of the complementarity determining regions (CDRs) of either monoclonal antibody 4D5 or monoclonal antibody 520C9.

As noted in the "written description" rejection above, Mariuzza et al (*supra*) reviews the structural basis of antigen-antibody recognition is reviewed. A naturally occurring antibody comprises two polypeptides, the so-called light and heavy chains. The antigen-combining site of an antibody is a three-dimensional structure, which fully comprises six "complementarity-determining regions" (CDRs), three each from the light and heavy chains. The amino acid sequences of the CDRs are hypervariable, as the amino acid residues contained within the CDRs determine much of antibody's antigen-binding specificity. Of the amino acid residues of the antibody contacting the antigen, six are within the light chain, nine are within the heavy chain, and two are within the constant or nearly constant "framework" regions.

Thus, an antibody comprising only one of the six CDRs of which either monoclonal antibody 4D5 or monoclonal antibody 520C9 is not reasonably expected to bind HER2, but if it were to do so, it would not necessarily bind the same epitope of HER2 as either of monoclonal antibody 4D5 or 520C9.

As further explained in the above rejection of the claims as failing to satisfy the written description requirement, the prior art teaches well-known and conventional methodology for "humanizing" monoclonal antibodies. For example, Gussow et al. (*supra*) teaches the general methodology for making humanized antibodies; see entire document. One means for producing a humanized antibody involves grafting the six CDRs from the light and heavy chain variable regions from a murine antibody into the framework of a human antibody. However, in general, if only one or two of the CDRs from either the light or heavy chain variable region were to be grafted, but not all three, the resultant antibody would not be expected to retain the binding affinity and specificity of the parent antibody.

Thus, while the prior art teaches some understanding of the structural basis of antigen-antibody recognition and conventional methodology for humanizing monoclonal antibodies, it is aptly noted that the art is characterized by a high level of unpredictability, since the skilled artisan still cannot accurately and reliably predict the consequences of amino acid substitutions, insertions, and deletions in the antigen-binding domains and surrounding framework regions of antibodies. For example, Giusti et al. (*supra*) teaches the specificity and affinity of an antibody is exquisitely sensitive to amino acid substitutions within the primary structure of the antibody, since only a single amino acid substitution in the heavy chain of an antibody completely altered the binding specificity of an antibody that binds phosphocholine, such that the altered antibody fails to bind phosphocholine but instead binds DNA; see entire document (e.g., the abstract). Chien et al. (*supra*) teaches that significant structural and functional changes in an antigen-binding site can be caused by amino acid substitutions in the primary structure of an antibody, including substitutions as a site remote from the complementarity determining regions of the antigen-binding domain; see entire document (e.g., the abstract). Similarly, but more recently, Caldas et al. (*supra*) teaches an unexpected effect of substituting a framework residue upon binding specificity during the humanization of an antibody that binds CD18; see entire document (e.g., the abstract).

So in response to Applicant's argument that specification would be sufficiently enabling of the claimed invention, there is a preponderance of factual evidence, now of record, suggesting the opposite would in fact be true. The skilled artisan could not make, and then use, the antibodies comprising only a CDR of monoclonal antibody 4D5 or 520C9 to which the claims are directed without undue and/or unreasonable experimentation.

Applicant has further argued, beginning at page 26 of the amendment filed February 15, 2007, that although Stancovski et al. teaches anti-HER2 antibodies that are not inhibitory, the majority of their antibodies are and the differences in their effects upon cells expressing HER2 are accounted for by differences in epitope specificity.

This argument is not persuasive; the teachings of Stancovski et al. indicate the art is unpredictable. Furthermore, as has already been extensively discussed in the

paragraphs above, the differential effects of the various different antibodies known in the art do appear epitope specific; and it is for precisely this reason that it is submitted that the instant disclosure would not be reasonably enabling of the claimed invention.

Applicant has contended that the Examiner has misrepresented the teachings of Lewis et al. as suggesting the murine monoclonal antibody 4D5 lacks efficacy, and the failure of the antibody to inhibit the growth of other types of cancer is irrelevant.

In response, the Examiner disagrees. Lewis et al. teaches murine monoclonal antibody is ineffective to induce ADCC. Furthermore, because Lewis et al. teaches murine monoclonal antibody 4D5 does not affect the proliferation of gastric and colon cancer cells, even though these cells express an amount of HER2 that is equivalent to the amount expressed by breast cancer cells that are sensitive to the effects of treatment with the antibody, it is apparent that is it not by mere virtue of the epitope to which an antibody binds that the antibody has anti-proliferative effects upon breast cancer cells expressing HER2.

Applicant has asserted that Keler et al. does not state that monoclonal antibody 520C9 does not mediate ADCC.

In reply, the Examiner disagrees. Keler et al. demonstrates the $F(ab')_2$ fragment of monoclonal antibody 520C9 is relatively incapable of mediating ADCC compared to MDX-H210, a recombinant bispecific antibody comprising a Fab' fragment of 520C9; see, e.g., page 4011, Figure 6.

Applicant has argued that, as evidenced by Stockmeyer et al. (2003), monoclonal antibody 520C9 is capable of mediating ADCC of human breast cancer cells in the presence of polymorphonuclear granulocytes.

In response, the claims are not solely directed to monoclonal antibody 520C9, but rather to any antibody that binds the extracellular domain of HER2, which comprises a CDR of either monoclonal antibody 4D5 or 520C9. Nonetheless, as explained in the preceding Office actions, even though the prior art teaches monoclonal antibody 520C9 is capable of mediating ADCC, its ability to do so appears relatively unique and its use *in vivo* to achieve therapeutic benefit in treating cancer overexpressing HER2 has

apparently not been reported; see, e.g., pages 14 and 15 of the preceding Office action mailed February 18, 2005.

Furthermore, it is again noted that, while Stockmeyer et al. (2003) discusses the results of *in vitro* studies, which were designed to further characterize the mechanism by which polymorphonuclear granulocytes induce cell death, Stockmeyer et al. does not establish the clinical or therapeutic effectiveness of monoclonal antibody 520C9. So, while the art teaches that an immunotoxin comprising this antibody can be used to inhibit the growth of tumor cells, there appear no reports that the monoclonal antibody itself, or any fragment thereof, is capable of effectively inhibiting the growth of tumor cells *in vivo*. Again, Keler et al. (of record) demonstrates the $F(ab')_2$ fragment of monoclonal antibody 520C9 is relatively incapable of mediating ADCC compared to MDX-H210, a recombinant bispecific antibody comprising a Fab' fragment of 520C9. Again, it is not by mere virtue of the epitope to which an antibody binds that the antibody has anti-proliferative effects upon cancer cells expressing HER2.

As explained previously, regardless of the specific epitope to which the anti-HER2 antibody binds, as further explained in the preceding Office actions, few *naked* antibodies have been described which are capable of achieving clinically or therapeutically significant benefits in treating cancer. Again, as mentioned above, Herceptin™ seems the notable exception, inasmuch as it has been shown clinically effective, alone and/or in combination with other anticancer drugs, to inhibit the growth of breast cancer characterized by the overexpression of HER2.

Applicant has argued that Masui et al. teaches antibodies may act by different mechanisms to inhibit the growth of cancer cells.

Admittedly, the artisan is only beginning to understand the many mechanisms by which antibodies, such as HERCEPTIN are used effectively to treat breast cancer. Indeed there are multiple different mechanisms; nonetheless, the art of record demonstrates that one cannot presume that an antibody that binds to the extracellular domain of HER2 will be effective. Some antibodies that bind the extracellular domain of HER2 promote tumor growth; some antibodies have no effect; other antibodies may inhibit the growth of certain types of cancer cells, but not others; still other antibodies

may inhibit the growth of cancer cells, but to widely varying extents, as the consequence, for example, of their epitope specificity and/or by their markedly different mechanisms of action. So, in response to Applicant's remark, it is thus not the fact that such antibodies have such different activities that the present claims are deemed unpatentable under 35 U.S.C. S 112, first paragraph, it is rather the fact that the specification would not reasonably enable the skilled artisan to practice the claimed invention to achieve the claimed therapeutic effect in patients afflicted with breast cancer using just any antibody that binds the extracellular domain of HER2 without undue and/or unreasonable experimentation. Moreover, it is not sufficient to have merely pointed out the obvious, i.e., that the antibody used must have anti-tumor activity; instead, were the requirements to have been satisfied, the specification would have provided ample guidance, direction and exemplification to enable the skilled artisan and would-be practitioner of the claimed invention to make, identify, and/or select the antibodies that are so useful without undue and/or unreasonable experimentation.

With reference to the citation of Kim et al., Applicant has remarked that it is unreasonable for the Examiner to have asserted that *in vitro* studies are completely unreliable.

In response, it is submitted that the Examiner has made no such assertion. The value of *in vitro* studies is well appreciated in the art, as are the limitations of those studies.

As noted in the preceding Office action and again above, Kim et al. concludes the results of the *in vivo* studies could not be explained by the results obtained from the *in vitro* studies, which suggests the antitumor effects of these antibodies might involve still other mechanisms not yet identified or understood. Nevertheless, Kim et al. teaches their results clearly indicate that the epitope specificity of antitumor antibodies, in addition to their isotypes, determines their ability to exert effective antitumor activity both *in vitro* and *in vivo* (page 433, column 1). Given the complexity and unpredictability made evident by the teachings of Kim et al., it is submitted that the skilled artisan could

not practice of the claimed invention without undue and/or unreasonable experimentation.

As to the value of such preclinical studies, even those using mice, for example, as opposed to cell lines, have their limitations. Very recently, Dennis (*Nature*. 2006 Aug 7; **442**: 739-741) reports, despite their present indispensableness, mouse models, such as xenografts, have only limited utility in predicting the clinical effectiveness of anticancer treatments; see entire document (e.g., page 739, column 2). Dennis explains there is a "laundry list" of problems associated with the use of mice to model human diseases, such as cancer (page 739, column 1). Accordingly, Dennis reports, "[a]lthough virtually every successful cancer drug on the market will have undergone xenograft testing, many more that show positive results in mice have had little or no effect on humans, possibly because the human tumours are growing in a foreign environment" (page 740, column 1). Therefore, quoting Howard Fine, Dennis concludes: " 'Mice are valuable but they are, after all, still mice' ", suggesting the best study subject will always be the human (page 741, column 3).

In addition, Kelland (*Eur. J. Cancer*. 2004 Apr; **40** (6): 827-836) has reviewed the reliability of the model in predicting clinical response; see entire document (e.g., the abstract). While the successful use of such models in cytotoxic drug development is conclusive, Kelland discloses that today there is far less focus on the development of such drugs (page 833, column 2); rather, the focus is upon the development of "molecularly-targeted", largely cytostatic drugs, such as those disclosed in the instant application, which may act in synergy with other drugs to selectively reduce or inhibit the growth of neoplastic cells (e.g., page 885). In particular, where such drugs are naked humanized antibodies that act through mechanisms such as ADCC, Kelland states the models are of limited value, because such mechanisms depend upon the recruitment of the host's (i.e., mouse) immune response, which differs from or is not reflective of that found in man (page 834, column 2). With such limitations of the xenograft model in mind, Kelland suggests that the case for using the model within a target-driven drug development cascade need to be justified on a case-by-case basis (page 835, column 1). Still, Kelland et al. does not altogether discount the usefulness of such models,

since, at present, "it is premature and too much a 'leap of faith' to jump directly from *in vitro* activity testing (or even in silico methods) to Phase I clinical trials (via preclinical regulatory toxicology)" (page 835, column 2). Kelland, however, does not advocate the use of a single xenograft model to exhort one to accept assertions of the effectiveness of treating multiple and different diseases using the same agent, as has been done in the instant application, since Kelland compels one to decide on a case-by-case basis whether such a model is suitable or not.

Finally, Saijo et al. (*Cancer Sci.* 2004 Oct; **95** (10): 772-776) recently reviewed the reasons for negative phase III trial of molecular-target-based drugs and their combinations; see entire document (e.g., the abstract). Saijo et al. discloses that while numerous phase III trials have been conducted upon the basis of promising preclinical data such as that disclosed in the instant application, few have yielded strongly positive results, and the majority of results have been negative (e.g., abstract). Saijo et al. discloses that there are problems in preclinical prediction of combined effects of anticancer drugs, and the results of preclinical prediction of combined effects have been very poor (page 773, column 2). Saijo et al. teaches many reasons for the poor predictability of combined effects (page 774, Table 6).

Applicant has pointedly disagreed with the Examiner's interpretation of the significance of the teachings of Vuist et al.

As explained above, Vuist et al. is cited as an example demonstrating the complexity, as well as the unpredictability in this area of the art. Vuist et al. teaches treatment of cancer cells with an antitumor antibody of the isotype IgG2a was therapeutically active by itself; however, Vuist et al. teaches IgG1 and IgG2b isotype variants of this antitumor antibody were not active alone to inhibit the growth of the cells. As noted, Vuist et al. speculates that in the presence of IL-2 the antitumor activity of the antibody of IgG2a isotype may involve both IL-2-induced ADCC activity of lymphocytes and IgG2a-restricted antitumor activity of monocytes/macrophages. Thus, contrasting other disclosures, such as Kim et al. (*supra*), Vuist et al. provides factual evidence that mere knowledge of the isotype of an antitumor antibody does not provide a fair indication that the antibody in combination with IL-2 will be capable of mediating ADCC

in vivo, so as to be therapeutically effective and useful in the practice of the claimed invention. Furthermore, it is has been submitted that the teachings of Vuist et al. suggest mere identification of anti-HER2 antibodies capable of inhibiting the growth of cancer cells will not provide reliable indication that the antibody can or cannot be used in combination with IL-2 to treat cancer *in vivo*, since Vuist et al. discloses effective treatment of cancer cells with antibodies, which were not effective alone, in the presence of IL-2.

Though Applicant believes this interpretation is unwarranted, it is believed that the additional teachings of Dennis et al. Kelland, and Saijo et al. provide a sound basis for such inferences with respect the lack of the sufficiency of the instant disclosure to reasonably enable the use of the claimed invention as required under 35 U.S.C. § 112, first paragraph.

Consistent with such conclusions, Kipps et al. (*J. Exp. Med.* 1985 Jan 1; **161** (1): 1-17) teaches antibodies of identical binding affinity and specificity, but which are comprised of distinct Fc domains, either have a varying ability to mediate ADCC or lack the ability all together; see entire document (e.g., the abstract). Kipps et al. found that for the antibody tested, the murine IgG2a isotype was the most effective in directing ADCC by human effector cells, whereas the murine IgG2b directed intermediate levels of ADCC activity, but IgG1 was *inactive*; see, e.g., the abstract. Thus, it cannot be merely sufficient to have described an antibody as comprising an Fc effector region, as not every Fc effector region will predictably act to mediate ADCC activity of an antibody.

Although specific to a different antigen, Campbell et al. (*Blood Reviews.* 2003; 17:143-152) teaches that the only CD20 antibodies that have been shown to be effective in depleting primate B cells *in vivo* are antibodies such as rituximab, tositumab and ibritumomab that retain a full complement of CDRs and an IgG1 Fc region and/or are radiolabeled so that they retain ADCC, CDC activity and/or are cytotoxic to the cells they target because of their radiolabel.

Similarly in the case of anti-HER2 antibody-mediated therapy, De Santes et al. (*Cancer Research* 1992; **52**: 1916-1923) discloses the results of a study in which the radiolabeled murine monoclonal antibody 4D5, which binds specifically to the

extracellular domain of HER2, was administered to an animal (abstract). De Santes et al. teaches, "[t]reating the animals with 400-700 μCi ^{131}I-4D5 caused a marked inhibition of tumor growth, although no mice were cured" (abstract). However, De Santes, et al. also teaches, "[u]nlabeled 4D5 had no effect on tumor progression in this model" (abstract). So, while it is appreciated that HERCEPTIN is effective, as explained above, it is not evident that any other *naked* antibody that binds to the extracellular domain of HER2, but which is not conjugated to a cytotoxic moiety (e.g., a radionuclide), or known to be capable of inducing ADCC and/or CDC *in vivo*, can be used in practicing the claimed invention to achieve the claimed therapeutic effect.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), there appears a preponderance of factual evidence of record indicating the amount of guidance, direction, and exemplification disclosed in the specification, as filed, would be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

It is again noted for clarity that claims 74 and 79 have not been rejected as lacking a reasonably enabling disclosure, because claim 74 is directed to the method of claim 12 for treating breast cancer characterized by the overexpression of HER2, wherein said anti-HER2 antibody is Herceptin™ (trastuzumab) and said IL-2 polypeptide comprises the amino acid sequence of SEQ ID NO: 1 or is des-alanyl-1, serine-125 human interleukin-2 (i.e., aldesleukin), whereas claim 79 is directed to the method of claim 63 for treating breast cancer characterized by the overexpression of HER2, wherein said anti-HER2 antibody is Herceptin™.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. The rejection of claims 12-15, 17, 22-26, 35-37, 52, 58, 63, 64, 66, 68, 73, 75, and 77 under 35 U.S.C. 102(b) as being anticipated by Fleming et al. (Abstract No. 710, Program Proceedings, American Society of Clinical Oncology, 35th Annual Meeting, 1999) (of record), as evidenced by Fleming et al. (*Clin. Cancer Res.* 2002 Dec; **8**: 3718-3727), is maintained.

Beginning at page 32 of the amendment filed February 15, 2007, Applicant has traversed the propriety of this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

As explained in the above discussion of the issue of priority, because claims 12-50, 52, 53, 55, 56, 58, 59, 61-73, and 75-78 are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure, the effective filing date of the claims that are rejected is May 14, 2001. Accordingly, Fleming et al. (1999) is prior art under § 102(b). Where a rejection constitutes a statutory bar, a declaration, such as the declaration submitted by Applicant, cannot be relied upon to obviate that rejection. Accordingly, the merit of the a declaration under 37 C.F.R. § 1.132 by Michael Caligiuri, Neal Meropol, and Robert Schlisky, which is aimed to establish that Fleming et al. (1999) is not prior art under 35 U.S.C. § 102(a), as it is not a publication by "others", as well as that of Applicant's argument, are presently moot.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. The rejection of claims 27-31, 53, and 59 under 35 U.S.C. 103(a) as being unpatentable over Fleming et al. (Abstract No. 710, Program Proceedings, American Society of Clinical Oncology, 35th Annual Meeting, 1999) (of record), as evidenced by Fleming et al. (*Clin. Cancer Res.* 2002 Dec; **8**: 3718-3727), in view of Meropol et al. (*Cancer Immunol. Immunother.* 1998; **46**: 318-326), is maintained.

Beginning at page 33 of the amendment filed February 15, 2007, Applicant has traversed the propriety of this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant has argued that Fleming et al. is not prior art.

As explained in the above discussion of the issue of priority, because claims 12-50, 52, 53, 55, 56, 58, 59, 61-73, and 75-78 are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure, the effective filing date of the claims that are rejected is May 14, 2001. Accordingly, Fleming et al. (1999) is prior art under § 102(b). Where a rejection constitutes a statutory bar, a declaration, such as the declaration submitted by Applicant, cannot be relied upon to obviate that rejection. Accordingly, the merit of the a declaration under 37 C.F.R. § 1.132 by Michael Caligiuri, Neal Meropol, and Robert Schlisky, as well as that of Applicant's argument, are presently moot.

Applicant has further argued that the secondary reference fails to describe elements of the invention.

In response, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

As explained in the preceding Office action, Fleming et al. teaches that which is set forth in the above rejection of claims 12-15, 17, 22-26, 35-37, 52, 58, 63, 64, 66, 68, 73, 75, and 77 under 35 U.S.C. §102(b).

Fleming et al. does not expressly teach administering "recombinant" IL-2.

Nevertheless, Meropol et al. teaches aldesleukin, or Proleukin™; see entire document (e.g., page 319, column 1). Meropol et al. teaches such "recombinant" IL-2 is well tolerated and effective to stimulate expansion of natural killer cells over a prolonged course of treatment. Meropol et al. teaches as a next step in developing their program, they are undertaking a study combining daily subcutaneous administered low-dose IL-2, intermediate-dose pulses, and a humanized anti-HER2 monoclonal antibody in patients with cancers that overexpress HER2 (page 325, column 1).

Aldesleukin is "recombinant" IL-2, otherwise designated "des-alanyl-1, serine-125 human IL-2"; see, e.g., the specification, page 29, lines 1-11(as originally filed).

Therefore, it would have been obvious to one ordinarily skilled in the art at the time the invention was made to have administered "recombinant" IL-2, or more particularly "des-alanyl-1, serine-125 human IL-2" (i.e., aldesleukin) together with Herceptin™ in practicing the process disclosed by Fleming et al. because Meropol et al. teaches such "recombinant" IL-2 is well-tolerated and effective to stimulate expansion of natural killer cells over a prolonged course of treatment, and moreover because Meropol et al. discloses studies using such a combination to treat patients afflicted with cancer characterized by overexpression of HER2 are already being undertaken. One ordinarily skilled in the art at the time the invention was made would have been motivated to do so to treat patients afflicted with breast cancer characterized by overexpression of HER2.

17. The rejection of claims 27-31, 53, 59, and 65 under 35 U.S.C. 103(a) as being unpatentable over Fleming et al. (Abstract No. 710, Program Proceedings, American Society of Clinical Oncology, 35th Annual Meeting, 1999) (of record), as evidenced by Fleming et al. (*Clin. Cancer Res.* 2002 Dec; **8**: 3718-3727), in view of U.S. Patent No. 4,863,726 A (of record), is maintained.

At page 34 of the amendment filed February 15, 2007, Applicant has traversed the propriety of this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant has argued that Fleming et al. is not prior art.

As explained in the above discussion of the issue of priority, because claims 12-50, 52, 53, 55, 56, 58, 59, 61-73, and 75-78 are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure, the effective filing date of the claims that are rejected is May 14, 2001. Accordingly, Fleming et al. (1999) is prior art under § 102(b). Where a rejection constitutes a statutory bar, a declaration, such as the declaration submitted by Applicant, cannot be relied upon to obviate that rejection. Accordingly, the merit of the a declaration under 37 C.F.R. § 1.132 by Michael Caligiuri, Neal Meropol, and Robert Schlisky, as well as that of Applicant's argument, are presently moot.

Applicant has further argued that the secondary reference fails to describe elements of the invention; additionally, Applicant has contended that the combination of the cited references would lead the artisan to a different invention.

In response, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

As explained in the preceding Office action, Fleming et al. teaches that which is set forth in the above rejection of claims 12-15, 17, 22-26, 35-37, 52, 58, 63, 64, 66, 68, 73, 75, and 77 under 35 U.S.C. §102(b).

Fleming et al. does not expressly teach administering "recombinant" IL-2.

Nevertheless, U.S. Patent No. 4,863,726 A (Stevens et al.) teaches that which is set forth in the preceding Office actions[3]; see entire document. In particular, Stevens et al. teaches a "recombinant" IL-2, which is designated "des-ala$_1$-IL-2$_{ser}$125 mutein"; see, e.g., column 8, lines 46-55; column 24, lines 50-61. Furthermore, Stevens et al. teaches monoclonal antibody 520C9, which is used to make an immunotoxin effective in combination with recombinant IL-2 to treat mice bearing tumor cells to which the antibody binds; see, e.g., columns 23-25, Example II.

Absent a showing otherwise, the "recombinant" IL-2 disclosed by Stevens et al. is the "des-alanyl-1, serine-125 human IL-2" to which the claims refer.

Therefore, it would have been obvious to one ordinarily skilled in the art at the time the invention was made to have administered "recombinant" IL-2, or more particularly "des-alanyl-1, serine-125 human IL-2" (i.e., "des-ala$_1$-IL-2$_{ser}$125 mutein") in practicing the process disclosed by Fleming et al. because Stevens et al. teaches such "recombinant" IL-2, when used in combination with antitumor monoclonal antibodies to treat patients afflicted with tumors to which the antibodies bind, is effective to cause tumor reduction and/or augment LAK activity and moreover it was well appreciated in the art at the time the invention was made that "recombinant" IL-2 is, for example, more cost-effectively prepared than non-recombinant IL-2. In addition, it would have been obvious to one ordinarily skilled in the art at the time the invention was made to have administered "recombinant" IL-2, or more particularly "des-alanyl-1, serine-125 human IL-2" (i.e., "des-ala$_1$-IL-2$_{ser}$125 mutein") in combination with an effective amount of an immunotoxin comprised of a humanized form of monoclonal antibody 520C9, as opposed to Herceptin™, because using an animal model Stevens et al. teaches the combination of such "recombinant" IL-2 and an immunotoxin comprised of the murine monoclonal antibody 520C9 is effective to treat tumors to which the antibody binds, and because Fleming et al. teaches administering humanized antibodies, as opposed to murine antibodies to patients, as it was well appreciated by one ordinarily skilled in the art at the time the invention was made that humanized antibodies are used preferentially in treating patients because they are less immunogenic than murine antibodies and can therefore be administered more safely to humans without the risk associated with administering murine antibodies. One ordinarily skilled in the art at the time the invention was made would have been motivated to do so to treat patients afflicted with breast tumors to which the immunotoxin comprised of the humanized.

---

[3] See, e.g., the Office action mailed March 14, 2003, section 20, beginning at page 16; and the Office action mailed February 18, 2005, section 14, beginning at page 19, and section 15, beginning at page 22.

18. The rejection of claims 16, 32-34, 55, 56, and 67 under 35 U.S.C. 103(a) as being unpatentable over Fleming et al. (Abstract No. 710, Program Proceedings, American Society of Clinical Oncology, 35th Annual Meeting, 1999) (of record), as evidenced by Fleming et al. (*Clin. Cancer Res.* 2002 Dec; **8**: 3718-3727), in view of U.S. Patent Application Publication No. 2003/0185796 A1, is maintained.

Beginning at page 34 of the amendment filed February 15, 2007, Applicant has traversed the propriety of this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant has argued that Fleming et al. is not prior art.

As explained in the above discussion of the issue of priority, because claims 12-50, 52, 53, 55, 56, 58, 59, 61-73, and 75-78 are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure, the effective filing date of the claims that are rejected is May 14, 2001. Accordingly, Fleming et al. (1999) is prior art under § 102(b). Where a rejection constitutes a statutory bar, a declaration, such as the declaration submitted by Applicant, cannot be relied upon to obviate that rejection. Accordingly, the merit of the a declaration under 37 C.F.R. § 1.132 by Michael Caligiuri, Neal Meropol, and Robert Schlisky, as well as that of Applicant's argument, are presently moot.

Applicant has further argued that the secondary reference fails to describe elements of the invention; additionally, Applicant has contended that the combination of the cited references would lead the artisan to a different invention.

In response, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

As explained in the preceding Office action, Fleming et al. teaches that which is set forth in the above rejection of claims 12-15, 17, 22-26, 35-37, 52, 58, 63, 64, 66, 68, 73, 75, and 77 under 35 U.S.C. §102(b).

In particular, Fleming et al. teaches administering Herceptin™ every two weeks prior to "intermediate-dose" pulses of IL-2, which are administered for 3 days every two weeks to activate effector cells.

Fleming et al., however, does not expressly teach administering the antibody within 6 days of the initiation of a treatment period, as recited in claims 16 and 67.

U.S. Patent Application Publication No. 2003/0185796 A1 (Wolin et al.) teaches administering an anticancer monoclonal antibody in combination with IL-2; see entire document (e.g., the abstract). Wolin et al. teaches the dosing and scheduling can vary, so long as the treatment regimen provides beneficial therapeutic effects; see, e.g., paragraph [0017]; and paragraphs [0026]-[0062]. For example, Wolin et al. teaches multiple treatment cycles of variable duration to maintain NK cell count above an acceptable threshold level, wherein the duration of IL-2 administration is a function of the IL-2 dosing regimen used; see, e.g., paragraphs [0017], [0035], [0039], and [0116]. Wolin et al. teaches initial and subsequent treatment cycles are not necessarily the same; see, e.g., paragraph [0054]. Wolin et al. teaches both IL-2 and the antibody are administered concurrently on the same day, either at the same time (i.e., simultaneous administration) or at different times (i.e., sequential administration, in either order), or sequentially on different days; see, e.g., paragraph [0033]. At paragraph [0032], Wolin et al. teaches:

> [T]he two-level IL-2 dosing regimen is initiated prior to initiating weekly administration of therapeutically effective doses of anti-CD20 antibody. In this manner, a first dose of IL-2 is administered up to one month before the first dose of anti-CD20 antibody is administered. By "up to one month" is intended the first dose of IL-2 is administered at least one day before initiating anti-CD20 antibody administration, but not more than one month (i.e., 30 days) before initiating anti-CD20 antibody administration. Thus, IL-2 administration can begin, for example, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days (i.e., 1 week), 10 days, 14 days (i.e., two weeks), 17 days, 21 days (i.e., 3 weeks), 24 days, 28 days (4 weeks), or up to one month (i.e., 30 days) before administering the first therapeutically effective dose of the anti-CD20 antibody.

At paragraph [0018], Wolin et al. teaches, "[a]dministering of these two agents together in the manner set forth herein provides for greater therapeutic effectiveness than can be achieved using either of these agents alone, resulting in a positive therapeutic response that is improved with respect to that observed with either agent alone" and "the

beneficial therapeutic effects of these agents can be achieved using lower cumulative dosages of IL-2, thereby lessening the toxicity of prolonged IL-2 administration and the potential for tumor escape". Wolin et al. teaches recombinant IL-2 is administered (e.g., Proleukin™); see, e.g., paragraphs [0056]-[0059]. In addition, Wolin et al. teaches different preparations of IL-2 may be formulated for use, including, for example, stabilized monomeric preparations and spray-dried preparations; see, e.g., paragraphs [0096]-[0100].

Therefore, it would have been obvious to one ordinarily skilled in the art at the time the invention was made to have administered Herceptin™ to the patient following the initiation of a treatment period on any day preceding the administration of the first "intermediate-dose" pulse, since Wolin et al. teaches combining a two-level IL-2 dosing regimen and an anticancer antibody dosing regimen in which the IL-2 dosing regimen begins at, for example, 1 day, 2 days, 3 days, 4 days, 5 days, or 6 days before administering the first dose of the antibody. One ordinarily skilled in the art would have been motivated at the time the invention was made to practice the process disclosed by Fleming et al. by administering the antibody within, for example, 6 days of administering the first dose of IL-2 to the patient, so as to determine which schedule provides maximum therapeutic effect and/or optimal efficacy.

19. The rejection of claims 18, 19, 38-40, 42-47, 61, 62, 69, and 70 under 35 U.S.C. 103(a) as being unpatentable over Fleming et al. (Abstract No. 710, Program Proceedings, American Society of Clinical Oncology, 35th Annual Meeting, 1999) (of record), as evidenced by Fleming et al. (*Clin. Cancer Res.* 2002 Dec; **8**: 3718-3727), in view of U.S. Patent Application Publication No. 2003/0185796 A1, as applied to claims 16, 32-34, 54, 55, and 67 above, and further in view of Sosman et al. (*J. Clin. Oncol.* 1993 Aug; **11** (8): 1496-1505), is maintained.

Beginning at page 35 of the amendment filed February 15, 2007, Applicant has traversed the propriety of this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant has argued that Fleming et al. is not prior art.

As explained in the above discussion of the issue of priority, because claims 12-50, 52, 53, 55, 56, 58, 59, 61-73, and 75-78 are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure, the effective filing date of the claims that are rejected is May 14, 2001. Accordingly, Fleming et al. (1999) is prior art under § 102(b). Where a rejection constitutes a statutory bar, a declaration, such as the declaration submitted by Applicant, cannot be relied upon to obviate that rejection. Accordingly, the merit of the a declaration under 37 C.F.R. § 1.132 by Michael Caligiuri, Neal Meropol, and Robert Schlisky, as well as that of Applicant's argument, are presently moot.

Applicant has further argued that the secondary reference fails to describe elements of the invention; additionally, Applicant has contended that the combination of the cited references would lead the artisan to a different invention.

In response, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

As explained in the preceding Office action, Fleming et al. teaches that which is set forth in the above rejection of claims 12-15, 17, 22-26, 35-37, 52, 58, 63, 64, 66, 68, 73, 75, and 77 under 35 U.S.C. §102(b).

U.S. Patent Application Publication No. 2003/0185796 A1 (Wolin et al.) teaches that which is set forth in the above rejection of claims 16, 32-34, 54, 55, and 67 are rejected under 35 U.S.C. 103(a).

However, none of the aforementioned references expressly teaches administering the antibody and IL-2 during an "introductory cycle", *per se*, which comprises daily administration of IL-2 through at least day 20 of the cycle and the administration of the antibody on day 7 of the cycle, as recited in claims 18, 42, and 69. Furthermore, none of the aforementioned references expressly teaches cycles of treatment that occur subsequently to such an "introductory cycle", which comprises

administration of the antibody at day 1 and daily administration of IL-2 through at least day 14, as recited in claims 19, 47, and 70.

Sosman et al. teaches a phase I clinical trial combining monoclonal antibody therapy and IL-2 therapy in which patients were initially treated during a 20-day cycle; see entire document (e.g., the abstract).

Therefore, it would have been obvious to one ordinarily skilled in the art at the time the invention was made to have administered Herceptin™ to the patient following the initiation of an "introductory cycle" of treatment lasting at least 20 days, which comprises administering IL-2 daily and administering the antibody on day 7 of the cycle, preceding the administration of the first "intermediate-dose" pulse, since Wolin et al. teaches combining IL-2 therapy with antibody therapy during variable courses of an extended multicycle treatment regimens, which are adjusted so as to provide maximum therapeutic effect and/or optimal efficacy, and Sosman teaches an initial or "introductory" cycle of 20 days, which similarly comprises administering an antibody and IL-2. Furthermore, it would have been obvious to one ordinarily skilled in the art at the time the invention was made to have followed such an "introductory" treatment cycle with subsequent cycles of at least 14 days comprising administering the antibody on the first day of the cycle and administering IL-2 daily, since Wolin et al. teaches treatment regimens comprising multiple cycles, which are not necessarily the same, and may comprise administering the antibody on the first day of such a cycle and administering IL-2 on a daily basis for periods of, for example, two weeks. One ordinarily skilled in the art would have been motivated at the time the invention was made to practice the process disclosed by Fleming et al. by administering the antibody on day 7 of, for example, an initial treatment cycle of at least a 20 days comprising daily administrations of IL-2 to the patient, just preceding the administration of the first "intermediate-dose" pulse of IL-2, and then follow such an initial treatment cycle with subsequent treatment cycles comprising administering the antibody on the first day and administering IL-2 daily, so as to determine whether such a schedule provides maximum therapeutic effect and/or optimal efficacy.

20. The rejection of claims 20, 21, 41, 48-50, 71, and 72 under 35 U.S.C. 103(a) as being unpatentable over Fleming et al. (Abstract No. 710, Program Proceedings, American Society of Clinical Oncology, 35th Annual Meeting, 1999) (of record), as evidenced by Fleming et al. (*Clin. Cancer Res.* 2002 Dec; **8**: 3718-3727), in view of U.S. Patent Application Publication No. 2003/0185796 A1 and Sosman et al. (*J. Clin. Oncol.* 1993 Aug; **11** (8): 1496-1505), as applied to claims 18 and 19 above, and further in view of Soiffer et al. (*Clin. Cancer Res.* 1996 Mar; **2** (3): 493-499), is maintained.

Beginning at page 36 of the amendment filed February 15, 2007, Applicant has traversed the propriety of this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant has argued that Fleming et al. is not prior art.

As explained in the above discussion of the issue of priority, because claims 12-50, 52, 53, 55, 56, 58, 59, 61-73, and 75-78 are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure, the effective filing date of the claims that are rejected is May 14, 2001. Accordingly, Fleming et al. (1999) is prior art under § 102(b). Where a rejection constitutes a statutory bar, a declaration, such as the declaration submitted by Applicant, cannot be relied upon to obviate that rejection. Accordingly, the merit of the a declaration under 37 C.F.R. § 1.132 by Michael Caligiuri, Neal Meropol, and Robert Schlisky, as well as that of Applicant's argument, are presently moot.

Applicant has further argued that the secondary reference fails to describe elements of the invention.

In response, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In addition, Applicant has argued that there is no motivation, nor any expectation of success suggested in the combination of the cited references.

In response to Applicant's argument, the Examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention, where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, as explained in the preceding Office action, Fleming et al. teaches that which is set forth in the above rejection of claims 12-15, 17, 22-26, 35-37, 52, 58, 63, 64, 66, 68, 73, 75, and 77 under 35 U.S.C. §102(b). In particular, it is noted that Fleming et al. teaches a regimen comprising daily administration of low-dose IL-2 followed by "intermediate-dose" pulses for 3 days every two weeks.

U.S. Patent Application Publication No. 2003/0185796 A1 (Wolin et al.) teaches that which is set forth in the above rejection of claims16, 32-34, 54, 55, and 67 are rejected under 35 U.S.C. 103(a).

Sosman et al. teaches that which is set forth in the above rejection of claims 18 and 19 are rejected under 35 U.S.C. 103(a).

However, none of the aforementioned references expressly teaches weekly administration of "intermediate-dose" pulses of IL-2 during the "introductory cycle" of at least 20 days on days 8-10, or during subsequent cycles of at least 14 days on days 1-3, as recited in claims 20, 21, 41, 48-50, 71, and/or 72.

Soiffer et al. teaches a regimen comprising an introductory "priming" cycle of daily administration of low-dose IL-2 followed by "intermediate-dose" pulses (i.e., boluses) for 5 days every week; see entire document (e.g., the abstract; and page 494, Figure 1).

Therefore, it would have been obvious to one ordinarily skilled in the art at the time the invention was made to have administered Herceptin™ to the patient following the initiation of an "introductory cycle" of treatment lasting at least 20 days, which comprises administering IL-2 daily and administering the antibody on day 7 of the cycle, preceding the administration of the first of three daily "intermediate-dose" pulses of IL-2

beginning on day 8 of the cycle, since Fleming et al. teaches a regimen comprising daily administration of low-dose IL-2 followed by "intermediate-dose" pulses for 3 days every two weeks, whereas Soiffer et al. teaches a regimen comprising an introductory "priming" cycle of daily administration of low-dose IL-2 followed by "intermediate-dose" pulses (i.e., boluses) for 5 days every week. Furthermore, it would have been obvious to one ordinarily skilled in the art at the time the invention was made to have followed such an "introductory" treatment cycle with subsequent cycles of at least 14 days comprising administering the antibody on the first day of the cycle, administering "intermediate-dose" pulses of IL-2 on days 1-3 of the cycle, and then after administering "low-dose" IL-2 daily, since, again, Fleming et al. teaches a regimen comprising daily administration of low-dose IL-2 followed by "intermediate-dose" pulses for 3 days every two weeks, Soiffer et al. teaches a regimen comprising an introductory "priming" cycle of daily administration of low-dose IL-2 followed by "intermediate-dose" pulses (i.e., boluses) for 5 days every week, and Wolin et al. teaches treatment regimens comprising multiple cycles, which are not necessarily the same, and may comprise administering the antibody and IL-2 on the first day of such a cycle. One ordinarily skilled in the art would have been motivated at the time the invention was made to do so in order to determine whether such a schedule provides maximum therapeutic effect and/or optimal efficacy.

As to Applicant's argument that there would not have been an expectation of success, the Examiner asks why not?

New Grounds of Rejection

21. Claims 12-23, 25-50, 52, 53, 55, 56, 58, 59, and 61-73 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "new matter" rejection.

Claims 12, 16, 17, 25, 31, 42, 52, 55, 58, 61, 63, 64, and 65 recite "ATCC Number CRL-10463" and "ATCC Number HB-8696".

At page 15 of the amendment Applicant has asserted that support for the amendment to the rejected claims is found in the specification at, e.g., page 21, lines 23-25; page 22, line 11, through page 23, line 25; and page 29, lines 15-17.

Contrary to Applicant's assertions it does not appear that the language of the rejected claims finds support in the originally filed specification. The terms "ATCC Number CRL-10463" and "ATCC Number HB-8696" are not found in the specification, including the claims, as originally filed.

This issue might be remedied if Applicant were to more clearly identify the particular disclosures, which are believed to provide the necessary written support for the language of the claims.

22. Claims 12-23, 25-50, 52, 53, 55, 56, 58, 59, and 61-73 are directed to the anti-HER2 monoclonal antibodies 4D5 and 520C9 produced by hybridoma cell lines deposited under ATCC accession numbers CRL-10463 and HB-8696, respectively.

The specification does not teach one to make these antibodies by, for example, disclosing their amino acid sequences or the polynucleotide sequences encoding their amino acid sequences. Furthermore, it is unclear if a cell line (e.g., a hybridoma) that produces an antibody having the exact structural and chemical identity as either anti-HER2 monoclonal antibody 4D5 or 520C9, as is produced by the deposited material to which the claims are directed, is known and publicly available, or can be reproducibly isolated without undue experimentation. Without access to a hybridoma or recombinant cell line producing the monoclonal antibodies to which the claims are directed, it would not be possible to practice the claimed invention, because it would not be possible to make the antibody.

The exact replication of the antibody or a cell producing the same antibody, the exact determination of its amino acid sequence and/or the exact determination of a polynucleotide sequence encoding it are unpredictable events.

The specification, as filed, makes no specific reference to the recited deposited materials to which the claims are directed.

There is insufficient assurance of record that all required deposits have been made and all the conditions of MPEP 608.01 (p)(c) are met.

If a deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit has not been made under the Budapest treaty, then an affidavit or declaration by Applicant or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature must be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth under 37 CFR §§ 1.801-1.809 have been met.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

Furthermore, as it does not already do so, the specification should be amended to provide requisite information regarding such deposits (i.e., specific reference to the deposited material by the name of the depository and its accession number, which further provides the depository's address and the date the deposit was made). See 37 CFR § 1.809 (d).

Allowable Subject Matter

23. Claims 74 and 79 would be allowable over the art of record if rewritten or amended to overcome the rejections under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action.

A trademark is used to identify a source of goods, and not the goods themselves; so the use of the trademark "HERCEPTIN" in the claims is not proper. However, the term "Trastuzumab" identifies these particular goods (i.e., a recombinant, humanized anti-HER2 antibody derived from the murine monoclonal antibody 4D5, which is well known in the prior art), and not the source of those goods. Similarly, the use of the trademark "PROLEUKIN" in the claims is not proper, but the term "des-alanyl-1, serine-125 human interleukin-2 (Aldesleukin)" identifies those particular goods (i.e., a recombinant IL-2 molecule of a particular structure known in the prior art), and not the source of those goods.

Accordingly, the following claim drafted by the examiner and considered to distinguish patentably over the art of record in this application, is presented to Applicant for consideration:

A method of treating a subject for a breast cancer characterized by overexpression of the HER2 receptor protein, said method comprising concurrent therapy with the recombinant, humanized anti-HER2 antibody Trastuzumab and the recombinant des-alanyl-1, serine-125 human interleukin-2 molecule Aldesleukin, wherein said concurrent therapy comprises administering to said subject at least one therapeutically effective dose of said Aldesleukin in combination with a dosing regimen for said Trastuzumab, wherein said dosing regimen for said Trastuzumab comprises administering to said subject at least one therapeutically effective dose of said Trastuzumab, wherein said therapeutically effective dose of said Trastuzumab is in the range from about 1.0 mg/kg to about 10.0 mg/kg and wherein said therapeutically effective dose of said Aldesleukin is in the range from about 0.5 MIU/m2 to about 4.0 MIU/m2.

Conclusion

24. No claim is allowed.

25. Applicant is advised that should claims 18 and 38-40 be found allowable, claims 43-46 will be objected to under 37 CFR § 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Primary Examiner
Art Unit 1643

slr
April 16, 2007